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Exploration of a zero-tolerance regime on cerebral embolism in symptomatic carotid artery disease

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Summary
Background: Current protocols stress the importance of short-term diagnosis and treatment in recent TIA or minor stroke. The risk of a recurrent event can be predicted with embolus detection. Studies have shown that the presence of micro-emboli is associated with an increased risk of recurrent events. We explored in our patient population the effect of a zero-tolerance regime for cerebral embolism on outcome.
Methods: Patients with a recent TIA or minor stroke were assigned to a study group or control group. Both groups were treated according to European Stroke guidelines, including prompt start of anti-thrombotic therapy, statins and short-term carotid arteries duplex scanning. The study group was subjected to TCD (Delica 9 series, Shenzen Delicate Electronics Co., LTD., China) embolus detection as soon as possible (EDS, SMT Medical, Wuerzburg, Germany). If emboli were detected, treatment was started immediately to stop cerebral embolization. This was achieved by either an altered drug regimen (clopidogrel) or angioplasty or carotid endarterectomy within one or two days. If carotid intervention was indicated in the control group, it was performed within two weeks, according to European guidelines.
Results: 133 patients were enrolled in the study with three months follow-up. 61 patients were subjected to the control group, 72 patients were enrolled in the study group. Recurrent events occurred in 10.2% and 3.0%, respectively ($p = 0.145$).
Conclusion: The current study shows a non-significant reduction in recurrent events in the study group. Probably sample size in this pilot study was insufficient to detect a significant decline. Nevertheless, the results show that embolus detection is feasible and the zero-tolerance regime may enhance the outcome of TIA and minor stroke patients. The findings support the start of a multicenter randomized trial to assess the clinical value of emboli detection in TIA and stroke care.

Introduction

The primary goals of the TIA and stroke services are two-fold: first to promote full recovery of patients with neurological deficits and secondly prevention of stroke

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recurrence. Stroke recurrence can be divided in early and late stroke recurrence. Recent literature has shown that early stroke recurrence is seen especially within the first two weeks after the ischemic event. Age, blood pressure, clinical presentation and duration of symptoms are known predictors of stroke recurrence in this patient group. Diagnostic procedures such as duplex of the carotid arteries and transcranial Doppler (TCD) of the middle cerebral artery may enhance the prediction of early stroke risk recurrence as high grade carotid artery stenosis in combination with ongoing cerebral embolism is a strong independent risk factor of stroke recurrence [1,2]. Although duplex examinations have been implemented in current stroke protocol for screening high-risk individuals, TCD embolus detection has till date not gained a prominent place in screening TIA and stroke patients to evaluate the stroke risk recurrence. Nevertheless there are a number of potential advantages of embolus detection in stroke care. First it may reassure embolus negative patients. Secondly it may speed up the process of source location and treatment in embolus positive patients and finally it may refine indications for carotid artery surgery. To evaluate the efficacy to prevent stroke recurrence of embolus detection in a clinical setting we designed this pilot study. Basically we explored the effect of a zero-tolerance regime for cerebral embolism on outcome. The gathered data may be used for future design of clinical trials that will prove or disapprove the value of embolus detection in TIA and stroke care.

Methods

Study design

To study the outcome patients with a recent (>6 weeks) carotid artery TIA or minor stroke were subjected to either a conventional duplex-guided protocol (control group) or a TCD embolus detection guided protocol (study group). Minor stroke was defined as a modified Rankin disability score between 0 and 2 [3]. The randomization of patients was not determined by chance but by availability of vascular technologist which could perform the TCD embolus detection (pseudo-randomization). Both groups followed the internationally accepted guidelines of the European Stroke Organisation [4]. This included a prompt start of an anti-thrombotic drug regime in every patient and a rapid (<48 h) duplex scanning.

Patients in the study group were subjected to a 30 min TCD embolus detection of the symptomatic middle cerebral artery to detect micro-embolic signals (MES). If patients showed positive embolism in relation to an unstable carotid artery stenosis, the carotid surgery or angioplasty was performed within 48 h. In case of positive embolism without a known embolic source clopidogrel was administered. If patients within the control group exhibit a symptomatic carotid stenosis or if patients in the control group exhibited a symptomatic carotid stenosis without MES, surgery or angioplasty was performed at the time interval advised by the guidelines of the European Stroke Organisation (within two weeks).

Patients contacted the hospital either by an admission at the emergency department or were referred by their house physician at the outpatient TIA and stroke clinic. Patients with an ischemic event of more than six weeks ago were excluded for this study. All patients were followed up for three months.

Treatment protocol

The protocol included a prompt start of an anti-thrombotic drug regime in every patient (300 mg acetylsalicylic acid for 14 days in case of a minor stroke or an initial dose of 300 mg acetylsalicylic acid on day 1 followed by a prescription of 100 mg daily in TIA patients). All patients underwent laboratory examinations, ECG, duplex examination of the carotid and vertebral arteries and a CT and/or MR of the brain. If duplex revealed a stenosis of more than 50% or the TCD embolus detection revealed active cerebral embolism a CT angiography was performed from the aortic arc including the basal arteries of the brain.

Therapeutic drug interventions included the prescription of anti-thrombotic drug such as acetylsalicylic acid in combination with dipyridamole acid (in case of atrial fibrillation: anti-coagulants), statines and anti-hypertensive treatment. Patients used clopidogrel for six months; in case of persistent cerebral embolization (for instance after carotid surgery or when cerebral embolism was still present after the administration of acetylsalicylic acid) the drug regimes were switched to a combination of anti-thrombotic drugs that more effectively reduced the level of cerebral embolism.

Carotid interventions

In case of a symptomatic carotid stenosis patients were asked to participate in the International Carotid Stenting Study (ICSS). The ICSS is an international multicenter trial which compares the efficacy of stenting versus surgery in the treatment of symptomatic carotid artery stenosis [5]. Patients scheduled for stent were treated with clopidogrel for at least six months, after carotid surgery they received acetylsalicylic acid and dipyridamole acid. Patients scheduled for surgery and stenting were observed for two days at the stroke unit.

Monitoring during stent procedure was done in awake patients by a neurologist. During carotid surgery the patients were exposed to general anesthesia and monitored by a clinical neurophysiologist. Monitoring techniques during surgery included both TCD and electro-encephalography. Based on monitoring results patients were electively shunted during the carotid endarterectomy. TCD monitoring was performed in all patients in the first hours after surgery and stenting procedures to detect persistent cerebral embolism or malignant cerebral hyperperfusion. All patients underwent a full neurological exam on regular time intervals after the stent or surgery until they were discharged from the stroke unit.

Data sampling

The following information on patient history was obtained: TIA and minor strokes we classified into the following categories: retinal TIA, cerebral TIA or stroke. Documented were the nature of the events such as visual, pure motor, pure sensory, dysarthria, dysphasia, ataxia, apraxia or combination of events. ABCD2 scores were obtained in all patients [6]. MRI findings were classified into cortical infarcts, subcortical infarcts and leucoaraiosis. Infarcts were further subdivided into recent or non-recent and left or right sided. The side, severity of the stenosis and presence of plaque ulceration on duplex and CTA were documented as well. Furthermore, blood pressure was documented as well as the current use of anti-thrombotic drugs or anti-coagulants. Documentation of the TCD embolus detection included: the side of insonation, the peak systolic-, mean and end-diastolic velocity, the duration of the measurement and the presence or absence of cerebral embolism by human experts. If experts found cerebral embolism the following parameters of that embolus were noted: velocity, phase of cardiac cycle (systolic/diastolic) in which the events occurred, intensity, duration and a parameter related to the musical characteristics of the embolus (the zero-crossing index) [7].

Data of stent procedures and surgery were prospectively documented including the occurrence of neurological or non-neurological complications. The follow-up at three month included a neurological visit at the outpatient clinic. Documented were the TIA and stroke recurrence rate. If complications had occurred in the post-operative phase of angioplasty or surgery they were evaluated including the occurrence of new medical events in the last three months.

All data were stored in a downloadable Internet based electronic management system which allowed online statistical analysis of all included case records. This data management system has been developed by Mediwebdesign© The Netherlands (http://www.mediwebdesign.nl/spi/stroke/loginreal.php).

Embolus detection by TCD

A TCD Delica 9 series (Delicate/Shenzen/China) equipped with a 2 MHz TCD transducer and a notebook PC (Acer®, Aspire 1800 Series) were used for this study. A special Delicate headband was used to hold the 2 MHz transducer, which allowed hands-off monitoring. The insonated artery was the middle cerebral artery at its origin, just lateral of the terminal internal carotid artery, on the ipsilateral side of the symptomatic carotid artery territory. Patients were monitored for 30 min. In case of positive embolism the other contra-lateral middle cerebral artery was examined to estimate whether the cerebral embolism was a uni-lateral or bilateral phenomenon. Insonation depth varied between 45 mm and 55 mm. Patients were asked to not speak or move their head during the monitoring session because angular or lateral probe movements may induce false positive embolic events.

To facilitate reliable embolus detection at the Haga Teaching Hospitals we developed an embolus detection system (EDS, SMT Medical, Wuerzburg, Germany) specially designed to detect the low intensity micro-embolic signal seen in TIA and stroke patients [7]. The EDS is a universal software package that can be used on every ultrasound system. On the basis of a neural network technology it classifies every intensity increase into MES or artefacts. The EDS allows full verification of the whole time series and has an export function which for instance allows consultation of a fellow colleague over the Internet. The final classification of the outcome of the EDS was done by two human experts which evaluated every event in both the embolus and artefact list. Human experts now decided whether the embolus in the embolus list was a true embolus or a false positive one. The same has been done for the artefact event list. In this list they searched for the presence of so called false negative embolus (which is an embolus in the artefact event list that has not been correctly classified by the EDS). On the basis of these examinations they finally decided: '*active cerebral embolism*' or '*no active embolism*'.

Table 1 Inclusion data of all patients.

Numbers	Study group 72	Control group 61
General aspects		
Age (yrs)	71.3	70.4
Ratio (female: male)	0.21	0.47
Modified Rankin score	0.59	0.61
Risk factors		
ABCD2 score	4.6	4.3
Clinical presentation		
Retinal events	17%	15%
Cortical events (aphasia)	30%	21%
Subcortical events (motor/sensory)	53%	64%
Duplex/CTA findings		
Carotid stenosis < 70% or no stenosis	72%	76%
Carotid stenosis > 70% or occlusion	28%	24%
Intervention		
Surgery or angioplasty	23%	30%

Statistical analysis

Categorical values were presented as numbers (percentages). Because of the limited number of observations statistical analysis were not supplied for Tables 1—4. Independent *t*-test was used to evaluate stroke and TIA recurrence for the control and the study group (whose distributions approximate normality). Statistical significance was considered at $P < 0.05$. SPSS (v 17.0) statistical software was used for statistical analysis.

Ethical aspects

Informed consent was given by all patients. They were explained about the observational nature of the study and were informed about the rapid and regular treatment regimes. They gave also consent for the three months follow-up monitoring. The study has been submitted to the Central Committee on Research involving Human Subjects but according to their guidelines ethical approval was not

Table 2 Epidemiological data of the study group.

Numbers	11	61
General aspects		
Age (yrs)	73	76
Male sex	55%	85%
Female sex	45%	15%
Modified Rankin score (mean)	0.36	0.45
Risk factors		
ABCD2 score (mean)	4.6	5.5
Clinical presentation		
Retinal events	27.3%	14.7%
Cortical events (aphasia)	27.3%	24.5%
Subcortical events	45.4%	63.8%
Duplex/CTA findings.		
Carotid stenosis > 70% or occlusion	72.7%	31.1%
CT/MRI findings		
Recent ipsilateral infarcts (%)	18.8%	22.9%

required for this study because the patients were not randomized into different treatment regimes. Merely patients were given the opportunity to participate in a new diagnostic procedure which was implemented at the Haga Teaching Hospitals. Both rapid and regular treatment protocols follow the current stroke guidelines of the European Stroke Organisation [4].

Table 3 Epidemiological aspects of the cerebral MES.

Embolic frequency TIA and stroke patients	Mean 3.4 (range 1—12)/30 min
Embolus characteristics	
Total number of MES	36
Mean intensity (dB)	3.8 (range 3.1—6.3)
Mean duration (ms)	35.7 (range 11.0—57.6)
Mean zero-crossing index	13.2 (range 2.6—40.2)
Mean velocity and (cm/s)	35.4 (range 10—53)
Ratio embolus in systolic and diastolic phase	1:12
Embolic sources	
Internal carotid artery origo stenosis	9 out of 11 patients
Carotid siphon stenosis	2 out of 11 patients
Cardiac source	0 out of 11 patients
Embolic activity 2—5 days after treatment	
Drug switch from Aspirin to Clopidogrel: complete disappearance in	2 out of 2 patients
Carotid surgery complete disappearance in	2 out of 2 patients
Carotid angioplasty complete disappearance in	7 out of 7 patients

Table 4 Outcome of the study group.

Embolic activity	Pos	Neg
Numbers	11	61
Timing of therapeutical intervention after EDS (days)	1.6[a]	14.0
Outcome at three month		
TIA recurrence rate	0%	1.6%
Stroke recurrence rate	0%	1.6%
Sum TIA and stroke rate	0%	3.2%

[a] Calculated for nine patients; two patients could not be treated within the time of 48 h.

Results

Baseline data

Patient inclusion started on 1.8.2008 to 31.12. 2009, the follow up was finished on 1.4.2010. 133 patients enrolled in the study with three months follow-up. 61 patients were subjected to the control group, 72 patients enrolled in the study group. All patients could be evaluated to establish outcome. Table 1 shows the data of both patient groups. The table shows that both groups have more or less similar basic demographic parameters. In the control group there is a preponderance of women compared to the study group. Age, modified Rankin scores, ABCD2 scores, clinical presentation, duplex findings and frequency of carotid surgery and/or angioplasty showed similar distributions.

Epidemiology of cerebral embolism

Table 2 gives specific data of the study group and shows the relationship between clinical data and the presence or absence of cerebral embolism. Table 2 shows that cerebral embolism in this patient cohort was associated with a high-grade internal carotid artery stenosis. Retinal events and aphasia were more frequently seen in patients who experienced cerebral embolism.

Table 3 shows the epidemiology of cerebral embolism. It showed a wide range of frequencies of emboli during the 30 min monitoring. Most emboli were short lasting, low intensity events that occurred in the diastolic phase of the cardiac cycle. The emboli had a very prominent musical sound expressed by the low zero-crossing index. The most prominent source of the embolus was an internal carotid artery stenosis. In most patients the internal carotid artery stenosis was located at the origin of the vessel. In two out of eleven patients the stenosis was located at the level of the carotid syphon. The embolic activity decreased after therapeutical interventions such as carotid surgery, angioplasty and a drug switch from aspirin to clopidogrel.

Outcome

Table 4 shows the outcome of the study protocol in relation to positive and negative embolism. Table 5 shows the outcome of both the control and study group. Table 4 shows

Table 5 Outcome for all patients.

Number	Study group 72	Control group 61	*p*-Value
Timing of therapeutical intervention after event (days)	24	22	
Angioplasty	11.2%	13.1%	
Carotid surgery	11.2%	14.8%	
Total number	22.4%	27.9%	
Outcome at three months			
Modified Rankin score (mean)	0.39	0.25	n.s.
TIA recurrence rate	1.4%	6.3%	
Stroke recurrence rate	1.6%	4.9%	
Sum TIA and stroke recurrence	3.0%	10.2%	0.145

that the diagnosis and treatment of patients with positive cerebral embolism was performed much faster than the diagnosis and treatment of patients without cerebral embolism. Stroke and TIA recurrence rate in both groups were very low (respectively 0.0% and 3.2%). In the study group, one patient experienced a stroke recurrence in the ipsilateral posterior cerebral artery resulting in a permanent hemi-anopsia. In the control group four recurrent strokes were observed. All these events occurred in the ipsilateral middle cerebral artery territory; two of these events occurred in the post-operative phase of carotid surgery. One of these events was classified as a possible cerebral hyperperfusion syndrome.

Discussion

Spencer was the first investigator who showed that detection of cerebral embolism was possible with TCD [8]. His initial study describes the ongoing cerebral embolism in patients scheduled for carotid surgery. Soon after his publication the first reports appeared about MES signals in TIA and stroke patients. In the last ten years a number of studies showed unequivocal that ongoing cerebral embolism in carotid artery disease is a strong independent predictor of stroke [1,2]. The current clinical study tried to explore the potential of embolus detection to enhance the outcome of patients with symptomatic carotid artery disease. Briefly summarized this study revealed a non-significant reduction in recurrent events in the study group. Probably sample size in this pilot study was insufficient to detect a significant decline. Nevertheless, the results show that embolus detection is feasible and the zero-tolerance regime may enhance the outcome of TIA and minor stroke patients. The findings support the start of a multicenter randomized trial to assess the clinical value of embolus detection in TIA and stroke care.

During this study we observed that some patients with a low ABCD2 score may exhibit ongoing cerebral embolism and other patients with high score ABCD2 scores did not always show cerebral embolism and vice versa. It seems that both methods could in a way be complementary as the EDS results are more indicative for plaque *stability* while some of the ABCD2 score components are more indicative for plaque *formation* (such as age, blood pressure and diabetes).

This study showed that EDS monitoring can be used for diagnosis and monitoring unstable carotid artery disease and gave insight in the epidemiology of cerebral embolism. MES were seen during the diastolic phase of the cardiac cycle and disappeared by anti-thrombotic drugs or plaques removal. The aforementioned aspects of the MES could best be explained by the hypothesis that these MES were generated by small solid particles that were disloged into the circulation by unstable carotid artery stenosis [9]. In some patients we noted >12 MES in 30 min which means that hundreds of these small particles must go to the brain within a 24 h timeframe. Only a minority of these micro emboli resulted in TIA's or minor strokes. It seemed that the normal brain has the capacity to clear these of tiny micro-emboli.

An important aspect is the duration of monitoring that is needed to detect emboli. Previous studies showed that embolism is non-continuous phenomenon so it might be that very short observation times result in false negative monitoring results. The present study however shows that 30 min of monitoring gives relevant clinical information which, in combination with a zero-tolerance regime can, reduce the stroke recurrence rate. If the frequency of embolism is high the observation time might be limited less than 30 min. We feel that the time that is needed to document at least two MES is the minimum time for embolus detection. Future studies with ambulatory TCD systems will focus on the value of extended embolus detection beyond the 30 min [10].

This study showed that therapeutical interventions could arrest ongoing cerebral embolism. This was observed after angioplasty, carotid stenting or after a drug switch to clopidogrel. The latter is in accordance with the CARESS trial [11] which showed that in patients with recently symptomatic carotid stenosis, combination therapy with clopidogrel and aspirin is more effective in reducing asymptomatic embolism.

Although the number of observation are small in the present study Table 4 indicates a trend that patients who experienced cerebral embolism have a different vascular profile than those who do not exhibit cerebral embolism. Embolus positive patients showed in contrast to embolus negative patients more retinal and cortical TIA in combination with a symptomatic high-grade carotid artery stenosis. Patients without cerebral embolism presented often a subcortical type of stroke or TIA and that these events are less often associated with a high-grade carotid artery stenosis. Therefore, it seems that embolus negative patients suffer more from a local thrombosis in relation to cerebral microangiopathy than carotid artery macro-angiopathy. However, micro-embolism may still play a role in genesis of microangiopathy in embolus negative patients. It is important to realize that TCD cannot detect very tiny embolic particles. The lower limit of TCD embolus detection is approximately about 0.3 mm [12]. The diameter of the origin of the perforating arteries of the brain is around 0.2—0.8 mm [13]. Thus lacunar strokes could be the result of sub 0.3 mm particles which cannot be detected by TCD. The second reason why embolus negative patients may experience an embolic stroke is that the source of the embolus is located more distal to the TCD sample volume. In this study the sample

volume was located around the origin of the MCA, while in lacunar stroke the emboli may for instance arise from unstable microvascular lesions of the perforating arteries which are located both distal and perpendicular to the sample volume. Therefore, the current TCD equipment will not answer the question whether very small emboli can cause lacunar and/or subcortical infarcts.

In summary at the HAGA Teaching Hospitals an embolus detection system (EDS) has been developed with a special focus to detect the short lasting, low intensity emboli which can be observed in TIA and stroke patients. The EDS can detect embolic activity in patients with a symptomatic carotid stenosis and can be used as a monitor to guard the safety and measure the efficacy of treatment. Reduction of cerebral embolism can be done by a number of interventions. Early prescription of anti-thrombotic drugs, carotid surgery or angioplasty is established means to arrest cerebral embolism. The outcome of the present study shows that with the EDS approach very low recurrence rate can be within range. The stroke recurrence rate at three months for TIA and minor stroke has decreased over the past ten years below the 5% level by the introduction of TIA and stroke services; however, much effort will be needed to achieve a further decrease. To achieve very low stroke recurrence rates (between 0% and 1%), patients need to be seen early after the event, high-risk individuals should be identified rapidly and delivery of anti-thrombotic drug regimes, surgery and angioplasty should be implemented without delay. Randomized clinical studies are needed to evaluate the clinical value of embolus detection in reducing the stroke recurrence rate in TIA and stroke patients.

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